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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,060	07/10/2000	Neil Andrew Williams	CTH-03	6761

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,060	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/19/04 has been entered.

2. Claims 83-100 are pending and are being acted upon in this Office Action.

3. Claims 84-88, 90-94 and 96-100 are objected to because "A" should have been "The" for said dependent claims.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 83-100 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims encompass a method of treating any subject for IgE mediated Type I allergies such as asthma, allergic cough, allergic rhinitis, conjunctivitis, atopic eczema, dermatitis, uticaria, hives, inset bit allergy, dietary allergy and drug allergy that are IgE mediated comprising administering to the subject a therapeutically effective amount of EtxB agent that binds to GM1, or if the agent is coadministered with antigen/allergen, the EtxB agent and the antigen/allergen are not coupled.

The specification discloses a method for screening agents capable of modulating ganglioside associated activity. The specification further discloses the use of GM1 binding agent such as Ctx, Etx, CtxB and EtxB in the manufacture of a medicament to affect an allergic condition and/or a hypersensitivity condition wherein the EtxB agent is not coupled to an antigen/allergen (page 28, line 26-30, page 29). The specification asserts that EtxB is effective

for treating allergy by blocking an IgE mediated response through modulation of a ganglioside associated activity.

However, the specification does not teach the "effective amount of EtxB agent" to be administered and by which route, i.e. mucosal, intravenous, intramuscular, or subcutaneous to all subject having *any* Type I allergy such as asthma, allergic cough, allergic rhinitis, conjunctivitis, atopic eczema, dermatitis, uticaris, hives, inset bit allergy, dietary allergy and drug allergies. Further, there is insufficient guidance as to the structure of the "antigen/allergen" to be coadministered with the EtxB agent without the amino acid sequence. Given the unlimited number of allergy, there is a lack of in vivo working example demonstrating that administering to any subject EtxB *alone or* EtxB and allergen (not coupled) is effective for inducing tolerance to all undisclosed antigen/allergen.

Kagan *et al*, of record, teach presently, the only available treatment of food allergies is dietary vigilance and administration of self-injectable epinephrine (abstract, in particular).

Wiedermann *et al,* of record, teach suppressive versus stimulatory effects of allergen/cholera toxoid (CtB) conjugates depending on the nature of the allergen in which murine model of type I allergy as well as the route of administration (See abstract, in particular). In the absence of guidance as to the structure of "antigen/allergen", the route of immunization and in vivo working examples, it is unpredictable which undisclosed antigen/allergen when coadminister to a patient is efficacious for inducing immune tolerance as a method of treating a subject for Type I allergies that are IgE mediated.

Herz *et al*, of record, teach allergens can differ in their immunogenicity as well as in their capacity to act as tolerogens (See abstract, page 274, nature of the antigen, in particular). Herz *et al* teach until now no mouse model has been available which resembles all of human bronchial asthma (page 272, column 2, Animal models of type I allergy and asthma, in particular). Each individual mouse strain demonstrates a unique response pattern following immunization of allergens. The same allergen causes different phenotype dependent on genetical prerequisites (page 273, column 1, in particular). Further, the route of allergen administration has important impact on the quality of the immune response (See page 273, column 2, in particular). Herz et al teach that dependence of experimental model and the antigen used, the effects as well as the mechanisms of action can vary which might indicate the complexity of predicting clinical consequences of any therapeutic approach (see page 279, in particular).

Tamura et al, of record, teach that the *physical association* of LTB and antigen such as OVA is required to mediate immune suppression (See page 228, column 1, Figure 2, in particular).

Hoynes et al teach that allergic sensitization is a Th2 process where Th2 T helper cells are more efficient in secreting IL-4, IL-5, and IL6 which promote the growth and differentiation of B cells and induce isotype class switching toward IgG1 and IgE in human (see page 180, col. 1, in particular). Hoynes et al teach successful treatment of allergy is accompanied by a *decrease* in Th2-type cytokine production and a concomitant switch to Th1 immune response (see page 180, col. 2, in particular).

Williams et al teach that co-administering ExtB agent that binds to GM1 not couple to antigen such as collagen type II (CII) to DBA mice *increases* IL-4 (Th2 immune response) with a concomitant reduction in interferon gamma (Th1 immune response) (see abstract, page 5291, Materials and methods, col. 2, first paragraph, in particular). Since allergic conditions and co-administering EtxB agent with an antigen are known in the art to promote Th2 response, it is not clear the claimed method is effective for treating any type I allergy that are IgE mediated using EtxB in the absent of in vivo working example.

For these reasons, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 10/19/04 and declaration by Neil Williams filed 12/20/02 have been fully considered but are not found persuasive.

Applicants' position is that claims have been amended to recite ExtB agent and Type I allergies have been limited to IgE mediated. As can be seen in Figures 3, 4 and 6 in the declaration by Neil Williams that treatment with EtxB reduces IgE levels and associated with IL-4 in a model for asthma and allergic rhinitis which are type I allergies that are IgE mediated. The

results further demonstrate that coadministration of EtxB with an antigen/allergen such as OVA, where the EtxB and the OVA are not conjugated.

In response, Hoynes et al teach that allergic sensitization is a Th2 process where Th2 T helper cells are more efficient in secreting IL-4, IL-5, and IL6 which promote the growth and differentiation of B cells and induce isotype class switching toward IgG1 and IgE in human (see page 180, col. 1, in particular). Hoynes et al teach successful treatment of allergy is accompanied by a *decrease* in Th2-type cytokine production and a concomitant switch to Th1 immune response (see page 180, col. 2, in particular).

Williams et al teach that co-administering ExtB agent that binds to GM1 not couple to antigen such as collagen type II (CII) to DBA mice increases IL-4 (Th2 immune response) with a concomitant reduction interferon gamma (Th1 immune response) (see abstract, page 5291, Materials and methods, col. 2, first paragraph, in particular). Since allergic conditions and co-administering EtxB agent with an antigen are known in the art to *promote Th2 response*, it is not clear the claimed method is effective for treating any allergy using EtxB in the absent of in vivo working example.

In response to the data shown in Figure 3 in the declaration by Neil Williams, there is insufficient evidence that the ova-specific IgE in the EtxB and Etx + Ova groups are statistically significant compared with control. Likewise, there is insufficient evidence that the Th2 cytokines such as IL-4 and IL-10 are significantly reduced with a concomitant increase in IFN-gamma as compared to the control. This conclusion is consistent with the lack of a reduction in IgG1 (Th2 response in mice) in Figure 7 and lack of an increase in IgG2a (Th1 immune response) as shown in Figure 8 and they are highly variable.

In contrast to applicant's assertion that Weidermann is not relevant to the enablement analysis because this paper was published after the filing date of the application and is therefore not prior art, applicant is reminded that this is an enablement, and not art rejection. It is noted that post-filing date references can be used as evidence of the state of the art existing on the filing date of the application. See MPEP 2164.05(a), including *In re Hogan*, 194 USPQ 527 (CCPA 1977) and *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). Such "postdate" Applicant's effective filing date is appropriate to serve as published art-recognized references to support the Examiner's position in the rejection and for showing the state of the art with regards to particular problems or known facts that indicate that a problem still exists or that treatments are still unpredictable in the art at a later date or even the present time.

In response to applicant's argument that the publication relates to CtxB conjugated to an antigen, Williams et al teach that co-administering ExtB agent that binds to GM1 not couple to antigen such as collagen type II (CII) to DBA mice *increases IL-4* (Th2 immune response) with a concomitant reduction interferon gamma (Th1 immune response) (see abstract, page 5291, Materials and methods, col. 2, first paragraph, in particular).

6. Claims 83-100 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "excluding non-IgE mediated inset bite allergies, dietary allergies, and drug allergies" in Claims 89 and 95 represents a departure from the specification and the claims as originally filed. The recitation of "excluding" appears to be a negative limitation. Adding the expressed exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts. See Ex parte Grasselli, 231 USPQ 393 (BPAI 1983).

"A method …EtxB that binds to GM1, wherein *if the agent is coadministered with an antigen/allergen the agent and the antigen/allergen are not coupled*" in claims 83 and 89 represents a departure from the specification and the claims as originally filed because the amended claims now imply that that EtxB agent can be administered with other antigen and if administering with other antigen, the EtxB agent can be coupled to other antigen.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 83-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"A method …administering …*EtxB that binds to GM1*, wherein *if the agent is coadministered with an antigen/allergen the agent and the antigen/allergen are not coupled*" claims 83 and 89 is indefinite because administering …EtxB that binds to GM1 without the antigen/allergen suddenly becomes *coadministered with an antigen/allergen*.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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